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FILE 'HOME' ENTERED AT 11:39:03 ON 18 MAY 2005

=> file .meeting
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=> (her2 antibody) and (her2 ced)
L1             0 FILE AGRICOLA
L2             0 FILE BIOTECHNO
L3             0 FILE CONFSCI
L4             0 FILE HEALSAFE
L5             0 FILE IMSDRUGCONF
L6             0 FILE LIFESCI
L7             0 FILE MEDICONF
L8             0 FILE PASCAL

TOTAL FOR ALL FILES
L9             0 (HER2 ANTIBODY) AND (HER2 CED)

=> (her2 antibody) and (her2 ecd)
L10            0 FILE AGRICOLA
L11            1 FILE BIOTECHNO
L12            0 FILE CONFSCI
L13            0 FILE HEALSAFE
L14            0 FILE IMSDRUGCONF
L15            0 FILE LIFESCI
L16            0 FILE MEDICONF
L17            0 FILE PASCAL
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TOTAL FOR ALL FILES
L18 1 (HER2 ANTIBODY) AND (HER2 ECD)

=> d l18 ibib abs total

L18 ANSWER 1 OF 1 BIOTECHNO COPYRIGHT 2005 Elsevier Science B.V. on STN
ACCESSION NUMBER: 1992:22224811 BIOTECHNO
TITLE: Antigen binding thermodynamics and antiproliferative effects of chimeric and humanized anti-p185(**HER2**) **antibody** Fab fragments
AUTHOR: Kelley R.F.; O'Connell M.P.; Carter P.; Presta L.; Eigenbrot C.; Covarrubias M.; Snedecor B.; Bourell J.H.; Vetterlein D.
CORPORATE SOURCE: Department of Protein Engineering, Genentech, Inc., 460 Point San Bruno Blvd.,South San Francisco, CA 94080, United States.
SOURCE: Biochemistry, (1992), 31/24 (5434-5441)
CODEN: BICHAW ISSN: 0006-2960
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1992:22224811 BIOTECHNO
AB The murine monoclonal antibody 4D5 (anti-p185(HER2)) inhibits the proliferation of human tumor cells overexpressing p185(HER2) in vitro and has been 'humanized' ¢Carter, P., Presta, L., Gorman, C. M., Ridgway, J. B. B., Henner, D., Wong, W.-L. T., Rowland, A. M., Kotts, C., Carver, M. E., and Shepard, H. M. (1992) Proc. Natl. Acad. Sci. U.S.A.(in press)! for use in human cancer therapy. We have determined the antigen binding thermodynamics and the antiproliferative activities of chimeric 4D5 Fab (ch4D5 Fab) fragment and a series of eight humanized Fab (hu4D5 Fab) fragments differing by amino acid substitutions in the framework regions of the variable domains. Fab fragments were expressed by secretion from Escherichia coli and purified from fermentation supernatants by using affinity chromatography on immobilized streptococcal protein G or staphylococcal protein A for ch4D5 and hu4D5, respectively. Circular dichroism spectroscopy indicates correct folding of the E. coli produced Fab, and scanning calorimetry shows a greater stability for hu4D5 (T(m) = 82 °C) as compared with ch4D5 Fab (T(m) = 72 °C). K(D) values for binding to the extracellular domain (ECD) of p185(HER2) were determined by using a radioimmunoassay; the ΔH and ΔC(p) for binding were determined by using isothermal titration calorimetry. ch4D5 Fab and one of the humanized variants (hu4D5-8 Fab) bind p185(**HER2**-**ECD**) with comparable affinity (ΔG° = -13.6 kcal mol.sup.-.sup.1). The enthalpy changes associated with binding, however, are considerably different (ch4D5 Fab ΔH = -17.2 ± 1.5 kcal mol.sup.-.sup.1; hu4D5-8 Fab ΔH = -12.9 ± 0.4 kcal mol.sup.-.sup.1), which suggests a significant difference in the mechanism of antigen binding. This difference may be important for antiproliferative activity since ch4D5 Fab retains activity whereas hu4D5-8 Fab is inactive. These results suggest that K(D) measurements alone are insufficient in an attempt to reproduce the activity of a murine antibody in a humanized form. Analysis of the thermodynamic data using an empirical method ¢Sturtevant, J. M. (1977) Proc. Natl. Acad. Sci. U.S.A. 74, 2236-2240! indicates that differences in the hydrophobic or vibrational contributions to binding cannot account for the observation of equivalent ΔG but differing ΔH. The hydrophobic contribution to antigen binding is equivalent for ch4D5 and hu4D5-8 Fab and is consistent with burial of about 960 Å.sup.2 of nonpolar surface area upon complex formation.

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	1	("20030219838").PN.	US-PGPUB; USPAT; EPO	OR	OFF	2005/05/18 11:31
L2	6	her2 same antibody same (her2 adj1 ecd)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2005/05/18 11:32